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Slowed luminance reaction times in cervical dystonia: disordered superior colliculus processing

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Abstract:

Background: Abnormal temporal discrimination in cervical dystonia is hypothesised to be due to disrupted processing in the superior colliculus. The fast, luminance-based, retino-tectal pathway, projects to the superior colliculus; chromatic stimuli responses, via the retino-geniculo-calcarine pathway, are up to 30ms longer.

Methods: In 20 cervical dystonia and 20 age-matched control participants, we compared reaction times to two flashing visual stimuli: (i) a chromatic annulus and (ii) a luminant, non-coloured annulus. Participants pressed a joystick control when they perceived the annulus flashing.

Results: Reaction times in control participants were 20ms significantly faster in the luminant condition than the chromatic ($p= 0.017$). Patients with cervical dystonia had no reaction time advantage in response to the luminant stimulus.

Conclusion: Cervical dystonia patients (compared to control participants) demonstrated no reduction in their reaction time to luminant stimuli, processed through the retino-tectal pathway. This finding is consistent with superior colliculus dysfunction in cervical dystonia. (149 words).

Introduction: Dystonia is characterised by sustained or intermittent muscle contractions causing abnormal repetitive movements and postures.[1] Adult onset idiopathic focal dystonia (AOIFD) is the commonest form of primary dystonia; cervical dystonia is the most prevalent phenotype.[2] The pathophysiology of AOIFD is considered to involve impaired inhibition at both motor and sensory levels in a complex network of basal ganglia, thalamic, cerebellar and brainstem structures.[3–6] Disordered sensory processing in AOIFD includes abnormalities in temporal discrimination, defined as the ability to differentiate two sequential stimuli as being separate in time.[7,8] An abnormal temporal discrimination threshold (TDT) has been suggested as a mediational endophenotype in AOIFD [9] and, due to its crucial role in sensory integration, we hypothesise that temporal discrimination is mediated by the superior colliculus, implicating the superior colliculus in the pathogenesis of AOIFD; however there is a paucity of evidence. Patients with cervical dystonia and their unaffected first-degree relatives with abnormal TDTs have reduced superior colliculus activation by fMRI, in response to a salient looming visual stimulus, when compared to healthy control subjects and unaffected first-degree relatives with normal TDTs. [10]

The superior colliculus is a midbrain structure involved in sensorimotor processing; its main function is the covert, "bottom-up" orienting of attention, (reflexive, automatic processing of salient stimuli), occurring within 100ms[11], generating saccades and head turns.[12–14] Of the ten known axonal pathways from the retina to the brain, two deal with the bulk of "visual traffic."[15] In the retino-geniculo-calcarine pathway, magnocellular, parvocellular and koniocellular neurones project from the retina to the visual cortex via the lateral geniculate nucleus. The second, retino-tectal pathway, projects directly from the retina to striatum opticum of the superior colliculus, where wide field sensory vertical neurons respond at short latency (<40ms) to luminance and moving stimuli. Achromatic, luminant contrast signals via the magnocellular, retino-tectal route are faster, while chromatic signals

reach the basal ganglia later after cortical processing.[16–18] Experimental reaction times are up to 30ms longer in response to chromatic, compared to luminance (achromatic/contrast) based, stimuli.[16,19,20] The experimental paradigm however, must be designed with good chromatic selectivity so as to minimise achromatic intrusions and bias the results.

Given the evidence of disrupted superior colliculus processing in cervical dystonia, we hypothesised, firstly, that cervical dystonia patients, in comparison to healthy control participants, would have impaired processing of retino-tectal signals in the superior colliculus, manifested as delayed reaction times to luminance stimuli. Secondly, that reaction times to chromatic stimuli, carried through the retino-geniculo-calcarine pathway would not differ between cervical dystonia patients and healthy participants.

Aims: In this work we examined reaction times to (i) luminance-based and (ii) chromatic stimuli in patients with cervical dystonia compared to age- and gender-matched healthy control participants.

Participants & Methods

Cervical dystonia Patients: Cervical dystonia patients were recruited from the specialist dystonia outpatient clinic; the diagnosis of primary cervical dystonia was made at the dystonia clinic by neurologists with expertise in movement disorders. Patients all had normal or corrected to normal visual acuity and normal colour vision by testing with Ishihara plates. All patients were receiving botulinum toxin injections and no other treatment; testing was carried out 12 weeks after the last injection.

Control Group: Healthy control participants were recruited from hospital staff and visitors to the hospital. Control subjects had a full medical history and examination by a

neurologist to assess for any evidence of a neurological disorder. All participants had normal or corrected to normal vision without any colour vision impairment using Ishihara testing and were on no medication.

Experimental Procedure: (full details in online supplementary methods file):

Participants were seated at a desk, with a joystick, facing a laptop screen in a darkened room.

Visual Display and Task: Participants first completed a ***calibration task*** prior to assessing reaction times. This calibrated an individual's unique luminance level at which they could detect 50% of the flashing stimuli during the reaction time task. ***Reaction time task:*** The participant was instructed to press the trigger as soon as possible after they saw a "flash" in the annulus on screen. Three repetitions were performed for each condition (luminant or chromatic) with 56 flashes presented during each trial. Mean reaction times for each stimulus condition were calculated from 168 test stimuli for each condition; the order of the two different stimuli presented was randomised between participants.

Statistical Analysis: An unpaired t-test was performed to assess the mean reaction times between groups for each condition. Statistics and plots were generated using RStudio (RStudio Team [2015]. RStudio: Integrated Development for R. RStudio, Inc., Boston, Massachusetts, USA). SPSS (IBM SPSS statistics version 25). The Bayes factor analysis provides a measure of evidence for one model versus another [21] here it is used to investigate evidence for the null hypothesis (that there is no difference between conditions) or the alternative hypothesis (that there is a difference between conditions). The JZS Bayes factor was computed using the R package Bayes Factor using the default effect size of 0.707 [22]. A JZS Bayes factor can be read such that a JZS Bayes Factor less than 1 favours the null hypothesis over the alternative hypothesis, while a JZS Bayes factor greater than 1 favours the alternative.

Ethics: This study was approved by the Medical Research Ethics Committee, at St Vincent's

University Hospital, Dublin, Ireland. All participants provided written informed consent.

Results

Participants: 20 patients with cervical dystonia (17 women) and 20 control participants (15 women) were enrolled. The mean age in the cervical dystonia group was 54.5 years (SD 9.1) (range 35-67 years) and 52.6 years (SD 9.3) (range 33-67 years) in the control group. There was no statistically significant difference in mean age between the groups (p=0.52).

Reaction time task: The mean and standard deviation of the reaction times for each condition (luminant, chromatic) and relative reaction times to account for any motor delays by group (patients with dystonia and control participants) are listed in **Table 1**. **Figure 1** shows the difference in relative reaction times between the chromatic and luminant conditions for each control participants (left) and participants with dystonia (right). An unpaired t-test of relative reaction times revealed a significant difference between the groups (t(38)= -2.26, p=0.02952, JZS Bayes factor=2.214). This was driven by the control group who were on average 20ms significantly faster in the luminant condition than the chromatic (t(19)=2.6156, p=0.017, JZS Bayes factor=3.30), which is similar to the finding of Thirkettle and colleagues.[23] On the other hand **patients with cervical dystonia had similar reaction times across conditions and did not exhibit faster reaction times in response to luminant stimuli as did control participants** (t(19)=-0.7742, p=0.4481, JZS Bayes factor=0.289). In the control group 16 of the 20 participants had faster reactions for the luminant condition, while patients with dystonia were split, with 8 having faster reaction times and 12 having slower reaction times, in the luminant condition. To test for group differences (cervical dystonia versus control) in each condition post-hoc t-tests were conducted. The unpaired t-test showed no significant difference in the chromatic condition (t(38)=0.726, p=0.473, JZS Bayes=0.294) nor in the luminant condition (t(38)=1.647, p=0.108, JZS Bayes=0.733). It should also be noted that, by

conducting the primary analysis on the within-participant difference, this accounts for within-participant related motor variance which could be a concern in participants with cervical dystonia. There was no difference in accuracy (i.e the number of stimulus flashes detected or "hit rate") between patients and control participants for each condition during the reaction time task (**supplementary table 2)** (luminant task t(38)=-1.272, p=0.211; chromatic task t(38)=-0.468, p=0.643).

Discussion: Control group participants, as predicted, displayed an advantage (significantly faster reaction times) in response to luminant stimuli, compared to chromatic stimuli, implying faster visual processing of these stimuli via the retinotectal pathway, confirming previous study results.[19,24] Patients with cervical dystonia had slower reaction times compared to control participants to both luminant and chromatic stimuli. However, importantly, cervical dystonia patients had no reduction in their reaction time (no reaction time advantage) using luminant stimuli processed through the retino-tectal pathway. A clear limitation of this pilot study is the small number of participants. Although these findings are of interest, they do not localise the cause of impaired luminance-stimulus processing in cervical dystonia. The differences found in this study in reaction times to luminance stimuli, between cervical dystonia patients and control participants, may reflect disorder in: (i) intrinsic collicular sensorimotor transformation (ii) the tecto-thalamo-striatal projection, (iii) the pausing of nigro-collicular inhibition (iii) the tecto-reticulospinal movement circuits, or (iv) the cerebello-tectal circuitry that provides the excitatory drive for the movement when nigrotectal output from the basal ganglia pauses. These findings are consistent with, and supportive of, our hypothesis of superior colliculus dysfunction in dystonia, with evidence of impaired superior colliculus activation, by fMRI, in cervical dystonia and their relatives with abnormal TDTs response to looming visual stimuli.[10] We consider that further interrogation of the role of superior collicular processing in cervical dystonia is warranted.

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Table and Figure legends

Table 1: Mean and standard deviation of reaction times, in response to Chromatic and Luminant visual stimuli, for 20 control group participants and 20 cervical dystonia patients. Note the significant shortening of reaction time in the control participant group with luminance stimuli compared to the chromatic stimuli (p=0.017); such "luminant advantage" is not observed in the cervical dystonia patients.

Group	Mean Reaction Time to stimulus ± SD (ms)		
	Chromatic	**Luminant**	**Luminant Advantage**
Control participants	**283.1 ± 55.0**	267.9 ± 50.0	**15.2 ± 25.96***
Cervical dystonia	**296.26 ±59.5**	**301.7 ± 76.5**	**-5.0 ± 31.35**

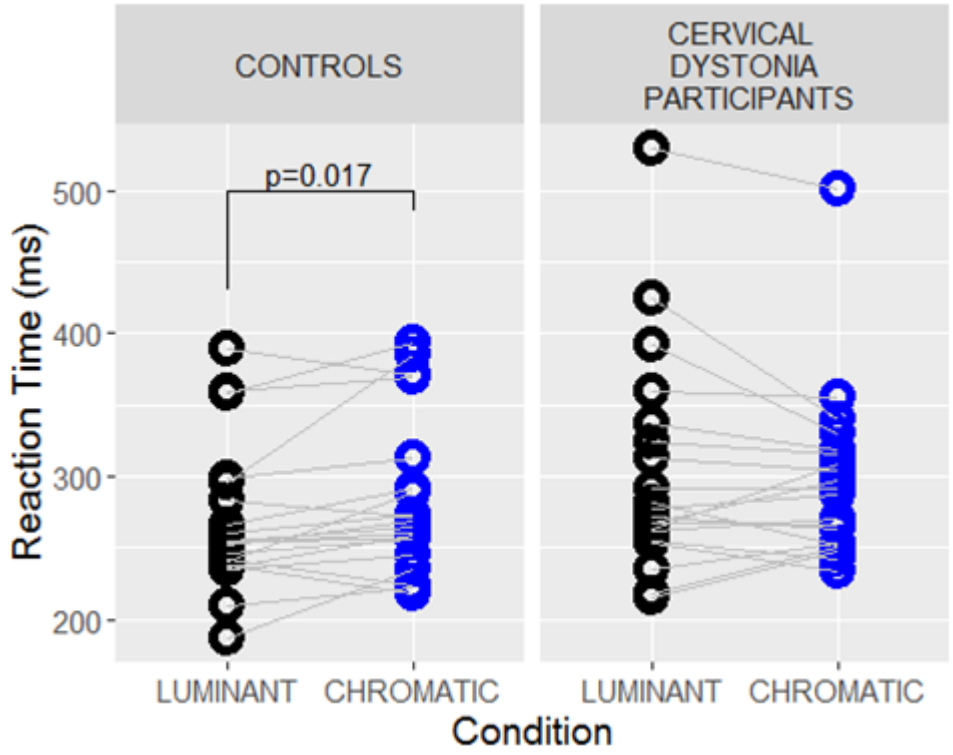

Figure 1: Scatter graph indicating, for each of the two groups, 20 healthy control participants (left) and 20 cervical dystonia patients (right), reaction times in response to chromatic visual stimuli and luminant stimuli. Note that reaction times for the control

patients are significantly shorter for luminant stimuli compared to isoluminant chromatic stimuli ($p = 0.017$). This shortening of reaction time in response to luminant stimuli is not observed in the cervical dystonia patients.

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